

Colon Sarcoidosis Responds to Methotrexate: A Case Report with Review of Literature

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Abstract

Sarcoidosis is a systemic disease with a 90% predilection for the lungs, but any organ can be involved. Sarcoidosis of the colon is rare. When this organ system is involved, it can be a feature of systemic disease or in isolated cases. Gastrointestinal sarcoid can resemble a broad spectrum of other disease processes, thus it is important for health care providers to be familiar with the various GI manifestations. Patients can have symptoms of fever, nausea, vomiting, unintentional weight loss, diarrhea, hematachezia, and severe abdominal pain. We report a case of sarcoidosis of the colon that responded to methotrexate and a MEDLINE search of 22 reported cases of colon sarcoid based on a compatible history and the demonstration of non-caseating granulomas. We describe the clinical manifestations of symptomatic colon sarcoid in relation to the endoscopic findings. Elevated serum ACE level, presence of CARD 15 mutations, and certain intestinal and extra-intestinal clinical features are helpful in differentiating between colon sarcoidosis and Crohn's regional ileitis. Steroids remain the mainstay of treatment, however methotrexate should be considered as alternative treatment.

Keywords: Sarcoidosis; Crohn's disease; Methotrexate; Serum angiotensin; Converting enzyme

Abbreviations: CARD: C Aspose Recruitment Domain; CT: Computed Tomography; HIDA: Hepatobiliary Iminodiacetic Acid; HIV: Human Immunodeficiency Virus; NF- κ B: Nuclear Factor kappa-light chain-enhancer of activated B cells; PPD: Purified Protein Derivative; SACE: Serum Angiotensin Converting Enzyme; Tc: Technetium

Introduction

Sarcoidosis is a systemic disease with a 90% predilection for the lungs, but any organ can be involved. Less than 1% has gastrointestinal tract involvement with the stomach being most commonly involved [1]. The esophagus, appendix, rectum, and pancreas are less frequently involved, while colonic sarcoidosis is rare. Clinical symptoms can mimic inflammatory bowel disease, Whipple's disease, and infectious granulomatous diseases. We report a case of colon sarcoidosis and review of the relevant literature to illustrate how symptoms of colon sarcoidosis may be subtle or mimic other more common diseases.

Case

A 58 year-old Caucasian woman presented with right upper quadrant abdominal pain, watery diarrhea and malaise of one-month duration. Basic laboratory analysis including, liver function tests were normal, but abdominal ultrasonography showed gall-bladder stones. The patient's abdominal pain subsided after a successful laparoscopic cholecystectomy, until the 5th post-operative day when the patient presented with fevers and vomiting. Abdominal Computed Tomography (CT) scan revealed normal post-operative bile duct changes and multiple 2.2 cm periaortic lymph nodes. White blood count, amylase, and lipase were all normal as were blood and stool cultures. Febrile episodes persisted despite empiric antimicrobial therapy. The combination of anemia and lymphadenopathy raised the possibility of an infection or malignancy. Both, skin Purified Protein-Derivative (PPD) test and HIV tests were negative. Biopsy of the periaortic lymph nodes and bone-marrow biopsy performed revealed non-caseating granulomas. Acid-fast bacilli and fungal stains and cultures remained negative (even after 8 weeks). The patient's condition continued to deteriorate with persistent fevers, diffuse abdominal pain, watery diarrhea and 20-pound unintentional weight loss. Upper endoscopy was normal, while colonoscopy revealed tiny granular lesions in the sigmoid region

with pathological features of non-caseating granulomas. Tests for Whipple's disease, acid-fast organisms, fungi, and foreign material were negative. Sarcoidosis was diagnosed after the exclusion of infectious processes and inflammatory bowel diseases. Serum measurements of Angiotensin Converting Enzyme (ACE) was 144 μ /mg protein and subsequently developed hypercalcemia (11.5 ng/mL). Prednisone 40mg daily was started, but due to irritability, uncontrolled hyperglycemia it was promptly tapered and weekly methotrexate was administered. She clinically responded with resolution of all complaints and normalizing laboratory values within 18 months.

Discussion

Sarcoidosis, multisystem disease, is diagnosed based on compatible history and demonstration of non-caseating granulomas in the absence of infectious processes. Making this diagnosis remains challenging. There is a wide range of symptoms along with the non-specific granulomatous lesions. Over 90% of patients have lung involvement with other frequent sites involving lymph nodes, liver, spleen, skin and eyes. Although gastrointestinal sarcoid involving the esophagus, stomach, gallbladder, liver, and pancreas have all been reported in small numbers, colonic involvement is rare.

Colon sarcoidosis may occur as a feature of systemic disease or in isolated cases. The differential diagnosis is extensive including, infectious granulomatous diseases (tuberculosis, histoplasmosis), syphilis, celiac disease, inflammatory bowel disease, Whipple's disease and carcinoma. Our medline search resulted in 22 well-documented cases of colon sarcoid published from 1949 to 2008. Included in our analysis is the case we present, totaling to date 23 cases [2-21]. The

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Author	Age/Sex/Race	Abd pain	Weight Loss	Diarrhea	Lung / Med	Liver	Spleen	Areas affected	Elevated SACE
Raven 1949	53/M/NA	Present	Present	Present	Absent	Absent	Absent	Total colon	NA
McFarlane 1955	53/M/W	Present	Absent	Present	Absent	Absent	Absent	Cecum	NA
Aaronson 1957	37/F/B	Absent	Absent	Absent	Present	Absent	Absent	Sigmoid, descending colon	NA
Gourevitch 1959	53/M/W	Present	Present	Present	Absent	Absent	Absent	Sigmoid	NA
Gould 1973	29/M/B	Present	Absent	Absent	Present	Present	Present	Rectum	NA
Mora 1980	32/M/B	Present	Present	Present	Absent	Present	Present	Rectum	NA
Konda 1980	31/M/B	Present	Present	Absent	Present	Present	Present	Rectum, sigmoid	NA
Kohn 1980	55/F/B	Absent	Present	Absent	Present	Present	Absent	Sigmoid	NA
Stephen 1981	36/F/NA	Absent	Absent	Absent	Present	Absent	Absent	Total colon	NA
Tobi 1982	60/F/NA	Absent	Absent	Absent	Present	Present	Present	Rectum	NA
Sprague 1984	60/F/W	Absent	Present	Present	Present	Present	Present	Total colon	Yes
Bulger 1988	48/M/W	Present	Absent	Present	Present	Present	Absent	Total colon	NA
Levine 1989	44/M/B	Present	Absent	Absent	Absent	Absent	Absent	Descending colon	NA
Naschitz 1990	44/M/NA	Present	Absent	Present	Present	Present	Absent	Sigmoid	Yes
Zech 1993	34/F/B	Absent	Present	Absent	Present	Present	Absent	Total colon	Yes
Hilzenrat 1995	57/M/B	Present	Present	Absent	Absent	Absent	Present	Rectum, sigmoid, transverse colon	NA
Author	Age/Sex/Race	Abd pain	Weight Loss	Diarrhea	Lung / Med	Liver	Spleen	Areas affected	Elevated SACE
Dumot 1998	46/F/NA	Present	Present	Present	Present	Absent	Absent	Sigmoid	Yes
Beniwal 2002	58/F/B	Present	Absent	Present	Inactive	Absent	Present	Rectum, sigmoid	Yes
Veitch 2004	47/M/WI	Absent	Absent	Absent	Present	Absent	Absent	Total colon	No
Sorrentino 2004	55/F/W	Present	Absent	Absent	Absent	Absent	Absent	Cecum	Yes
Shigemitsu 2007	58/F/W	Present	Present	Present	Absent	Absent	Absent	Sigmoid	Yes
Beniwal 2008	58/F/B	Present	Absent	Present	Present	Absent	Absent	Rectum and Descending colon	Yes
Total (n=22)	Mean Age=47.1 years M:F=1:1 B=9 W=6 NA=5 WI=1	66.7%	47.6%	47.6%	57.1%	42.9%	33.3%	Sigmoid:71.4% Rectum:57.1% Cecum:38.1% Total colon:28.6%	87.5%

M=Male, F=Female, AA=African American, W=White, NA=Not Assessed, WI=West Indian, Abd=Abdomen, Med=Mediastinum, SACE=Serum Angiotensin Converting Enzyme.

Table 1: Summary of case reports on colon sarcoidosis.

findings are summarized in Table 1. These 23 patients have an equal gender predilection. Mean age is 47.1 years (range of 29 – 60 years) higher than the mean age generally reported for systemic sarcoidosis [22]. African-Americans appear to be most affected; however, in five cases patient ethnicity was not disclosed.

Patients having colon sarcoid generally present as having one or more of the following symptoms; fever, nausea, vomiting, unintentional weight loss, diarrhea, hematachezia, and severe abdominal pain. Fever and hematachezia were highly associated to recto-sigmoid regional involvement. Anemia was evident only in the presence of hematochezia. Despite abdominal pain (66.7%), unintentional weight loss (47.6%), diarrhea (47.6%) being the most common symptoms, they did not correlate with localized involvement. None of the clinical symptoms correlated with corresponding gross endoscopic features (ulcerative lesions, polypoid lesions, and either localized or diffuse infiltrative inflammation). Approximately half the patients with colon sarcoidosis in this series had a pre-existing diagnosis of sarcoidosis with lung and mediastinum involvement in 57%. Other corresponding sites included generalized lymph nodes (47.6%); liver (42.9%); spleen (33.3%); chronic skin changes [ichthyosiform lesions and lupus pernio, none with erythema nodosum] (23.8%); eyes (14.3%); nervous system (14.3%); parotid gland (9.5%); and bone marrow (9.5%). In rest of the cases, the diagnosis was confirmed after exclusion of infections and inflammatory bowel diseases. SACE levels when available are useful as the sensitivity ranges from 58% to 86% and specificity as high as 90% in sarcoidosis [23,24]. In contrast, many studies investigating SACE levels in Crohn's

disease found it to be normal or low [23-29]. Seven of 8 cases reviewed that measured SACE had elevated levels (87.5%). The one case where SACE level was normal, sarcoidosis was diagnosed on the basis of the presence of bilateral hilar adenopathy and Bell's palsy [20].

Compared with other types of non-pulmonary sarcoidosis cases, where lung and mediastinal involvement remains common, liver and spleen involvement appears to be more common in the presence of colon sarcoidosis. In a large case controlled study of sarcoidosis, liver and spleen involvement were 11.5% and 6.7% respectively [22]. Although our study consists of a small number of patients, these differences are of interest to postulate why liver and spleen may have been more involved compared to other types of sarcoidosis. Due to the rarity of colon sarcoidosis, it is unclear if antigen(s) stimulating granulomas in the colon also stimulate a similar host response in the liver and spleen.

Differentiating colon sarcoid from other diseases is challenging, particularly Crohn's disease, since both are granulomatous diseases with similar extra-intestinal manifestations. Both can exhibit erythema nodosum, pulmonary fibrosis, uveitis, renal stones, and arthropathies. One case even found an elevated CD4/CD8 ratio from bronchoalveolar lavage in a patient with Crohn's disease [30]. Cardinal features differentiating these two diseases are summarized in Table 2. Gross visualization and histological features can also be helpful. Gross visualization of colonic involvement of sarcoidosis includes; multiple nodules/polyps/masses (34.7%), friable and edematous mucosa (13%), aphthous erosions (8.9%), granularity (8.9%), normal mucosa (8.9%) or strictures (4.3%). The sigmoid colon (65%) and rectum (52.2%) are

	Ocular Involvement	Pulmonary Involvement	Mediastinal Involvement	Elevated SACE	CARD 15 mutations	Necrotizing Granuloma	Fistula Formation	Common Area
Colon sarcoidosis	May occur	Common	Common	Common	Rare	May occur	Absent	Sigmoid
Crohn's disease	Rare	May occur	Absent	Absent	Common	Rare	May occur	Ileocecum

Table 2: Cardinal features of colon sarcoidosis and Crohn's disease. SACE=Serum Angiotensin Converting Enzyme.

the most commonly affected area while the cecum is affected in 34.8%. Total colonic involvement was seen 7 cases. Endoscopic finding for Crohn's disease show irregular nodular appearance with hyperemia and focal erosions. The inflammation tends to be discontinuous throughout the bowel. Histologically, both diseases usually exhibit non-necrotizing granulomas, but in sarcoidosis, the non-casesating granulomas are seen without much inflammation or crypt abscesses. Morphological findings in active Crohn's disease include patchy edema, crypt disarray and intense transmural inflammation overshadowing granulomatous centers. While necrosis is rare, small patchy foci of necrosis may be seen in sarcoidosis [31].

Pathogenesis of sarcoidosis and Crohn's disease is quite similar with mediation through T_H-1 cytokines [32]. Recent studies shed some light into the genetic heterogeneity of these granulomatous disorders with particular interest in mutations of CARD 15, a protein with an important role in innate immunity. This mutation alters host response to structural components of microorganisms, in turn interfering with downstream activation of NF- κ B and ultimately contributing to granulomas formation. 43% of patients with Crohn's disease have have at least one of three CARD 15 mutations whereas this mutation has no association with non-familial sarcoidosis [33,34].

With a better understanding of this condition, it has been determined that treatment is not indicated in all cases. However, if it deemed clinically appropriate, corticosteroids remain mainstay of therapy for pulmonary and extra-pulmonary cases of sarcoidosis. Early case reports (6 cases) were treated with surgical resection due to the suspicion of malignancy. With the advent of improved diagnostic modalities and SACE levels, surgical resection for colonic sarcoidosis has become rare. Ten cases of the colon sarcoid cases were treated with corticosteroids and a majority had favorable response. As in our case, methotrexate is a suitable alternative agent in acute flares [35]. Although other cytotoxic agents (eg. azathioprine mycophenolate), have been useful, the body of evidence is not as strong as methotrexate. Biological agents, such as infliximab, have also been evaluated with various successes in different organs involved with sarcoidosis. These agents are being utilized in refractory cases and the duration of therapy is limited because of long-term sequele. The only death reported was a result of miliary tuberculosis after initiation of infliximab, despite careful exclusion of a prior infectious etiology [21]. Fortunately, there are no reports of death directly related to colon sarcoidosis.

Conclusion

Colon sarcoidosis is a rare phenomenon, even in patients with established diagnosis. The most important steps in diagnosing colon sarcoidosis are with careful exclusion of other potential granulomatous diseases, specifically Crohn's disease. Crohn's disease shares similar extra-intestinal manifestations to sarcoidosis. SACE level, CARD 15 mutation, the gross and histological features may aid the physician to reinforce their diagnosis. Prognosis of colon sarcoidosis appears to be favorable with medical treatment alone. For patients who require treatment, corticosteroids remain the hallmark of therapy with methotrexate as an effective alternative treatment. Fortunately, no direct causes of death have been accounted from colon sarcoidosis.

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